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Copper-Catalyzed Carboxylation of Alkenylzirconocenes with Carbon Dioxide Leading to *α,β*-Unsaturated Carboxylic Acids

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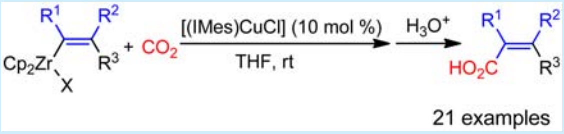
Supporting Information

ABSTRACT: A variety of alkenylzirconocenes were efficiently carboxylated by CO_2 utilizing the (IMes)CuCl catalyst yielding the corresponding *α,β*-unsaturated carboxylic acids in good yields. This reaction could be carried out in a one-pot operation via sequential carbozirconation of alkynes and carboxylation using CO_2 as starting materials under room temperature.

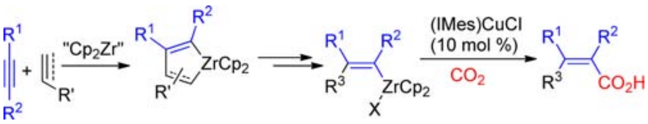


α,β-Unsaturated carboxylic acids are important scaffolds widely existing in pharmacologically and biologically active molecules.[1] In addition, *α,β*-unsaturated carboxylic acids have also been employed as useful building blocks in organic synthesis.[2] Owing to the importance of the *α,β*-unsaturated carboxylic acids, various synthetic methodologies for their synthesis have been developed. Traditional methods to yield the *α,β*-unsaturated carboxylic acids include utilization of named reactions such as the Doebner−Knoevenagel reaction,[3] Wittig reaction, and Horner−Wadsworth−Emmons reaction.[4] Although significant contributions have been made, use of a strong base or the formation of a considerable amount of organophosphorous byproducts such as phosphine oxides and phosphate salts in these reactions are unavoidable. Recently, the *α,β*-unsaturated acids have also been yielded from aldehydes and dibromoacetic acid with the assistance of an excess amount of SmI_2.[5] Most of the above-mentioned reactions are noncatalytic and less stereoselective.

Carbon dioxide (CO_2) is an attractive, abundant, inexpensive, and nontoxic one-carbon source. The utilization of CO_2 as a starting material in organic synthesis has received much attention.[6] In concept, addition of CO_2 to alkynes could serve as an efficient synthetic route for construction of the *α,β*-unsaturated carboxylic acids. Recently, transition-metal-mediated hydrocarboxylation of alkynes with CO_2 have been widely reported to provide disubstituted *α,β*-unsaturated carboxylic acids.[7,8] However, carbocarboxylation of alkynes with CO_2 to afford trisubstituted *α,β*-unsaturated carboxylic acids has been rarely reported, although methylcarboxylations and allylcarboxylation of alkynes with CO_2 have been reported.[9]

It is well-known that the carbometalation reaction of alkynes can be achieved in a regio- and stereospecific fashion. Various alkenylmetal species with well-controlled configurations could be generated in this way, which can serve as carbon nucleophiles for further formation of functionalized olefins. Recently, Ma and co-workers reported the Ni-catalyzed methylcarboxylation of alkynes with $ZnMe_2$ and CO_2 to afford *α*-methylene-*γ*-butyrolactone through a methylzincation/carboxylation tandem reaction.[10] More recently, Hou and co-worker reported that a combination of the methylalumination of alkynes with carboxylation of the resulting alkenylaluminum species with CO_2 provides a useful protocol for the synthesis of a variety of the *α,β*-unsaturated carboxylic acids.[8b] All of these reactions are still limited for introduction of a methyl group to the *β*-position of the *α,β*-unsaturated carboxylic acids. On the other hand, Rh-, Ni-, Cu-, and Ag-catalyzed carboxylation of alkenylboronic esters with CO_2 have been developed.[11] As part of our studies involving alkenylzirconocene chemistry,[12] we herein describe a sequential carbozirconation of various alkynes through zirconacycles and subsequent copper-catalyzed carboxylation of the resulting alkenylzirconocenes with CO_2 to afford a wide range of trisubstituted *α,β*-unsaturated carboxylic acids (Scheme 1).

Scheme 1. Formal Carbocarboxylation of Alkyne by a Tandem Carbozirconation/Carboxylation



As we have known, the transmetalation of the C−Zr bond into the C−Cu bond has been reported and numerous C−C bond formation reactions have been developed.[13] These results encouraged us to examine the carboxylation of alkenylzirconocene species with CO_2 utilizing copper catalysts. At first, we examined exclusive CuCl-catalyzed carboxylation of the alkenylzirconocene species **2a**, prepared by the ethanolysis of the corresponding zirconacyclopentene generated from 3-hexyne **1a** and Cp_2ZrEt_2,[14] with CO_2 (1 atm). The desired

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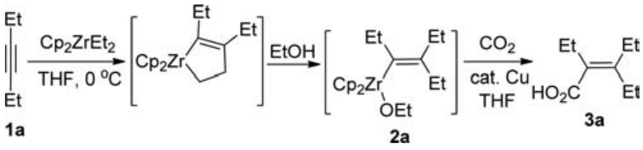
reaction did not proceed, even at 50 °C (Table 1, entries 1–2). When a copper complex (IPr)CuCl prepared by the reaction of CuCl and IPr (IPr = 1,3-bis(2,6-diisopropenyl)imidazol-2-ylidene)[15] was used as a catalyst, the carboxylation of **2a** with CO_2 proceeded smoothly at room temperature for 24 h to afford the carboxylic acid product **3a** in 60% yield (Table 1, entry 3). Furthermore, the use of the (IMes)CuCl (IMes = 1,3-dimesitylimidazol-2-ylidene) catalyst instead of (IPr)CuCl led to a higher yield (86%) of **3a** (Table 1, entry 4). Notably, in contrast with the transition-metal-catalyzed carboxylation of alkenylboron compounds,[11] this carboxylation of alkenylzirconocene did not require an additional base. It is also noteworthy that no carboxylated product was observed in the absence of any copper catalyst in this reaction.

Table 1. Carboxylation of Alkenylzirconocene 2a with CO_2 by Various Cu Catalysts[a]



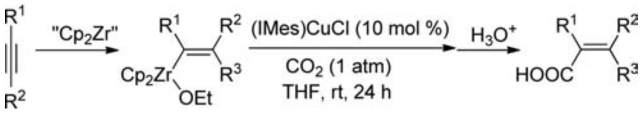
entry	catalyst	temp/°C	yield/%[b]
1	CuCl	rt	–
2	CuCl	50	–
3	(IPr)CuCl	rt	60
4	(IMes)CuCl	rt	86 (70)

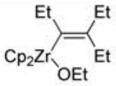
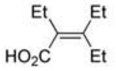
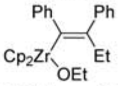
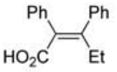
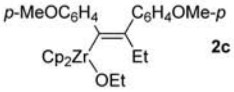
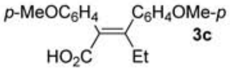
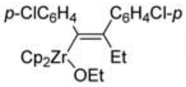
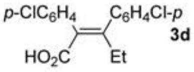
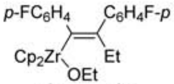
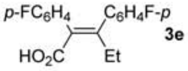
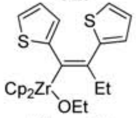
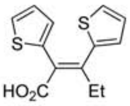
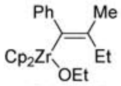
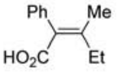
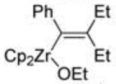
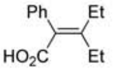
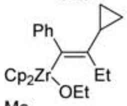
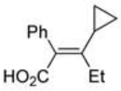
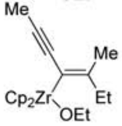
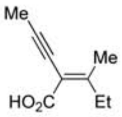
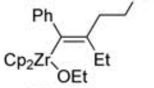
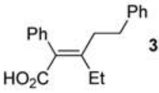
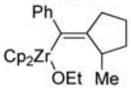
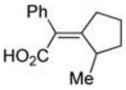
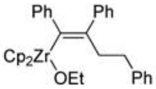
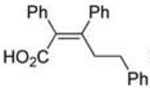
[a] Reaction conditions: alkenylzirconocene **2** prepared *in situ* from alkyne (0.5 mmol), Cu-catalyst (0.05 mmol), room temperature, 24 h. [b] NMR yield; isolated yield was shown in parentheses.

We then examined the carbocarboxylation of a variety of the alkenylzirconocene species with CO_2 by using (IMes)CuCl. Representative results are summarized in Table 2. The alkenylzirconocenes **2a**–**2m**, which were prepared by alcoholysis of *in situ* generated zirconacyclopentenes,[16] can tolerate various substituents such as alkyl, aryl, alkynyl, thienyl, and cyclopropyl groups. In all cases, the corresponding β-alkyl-α,β-unsaturated carboxylic acids **3a**–**3m** were formed in 49% to 77% isolated yields (entries 1–13).

Various preparative methods of alkenylzirconocenes are now available, such as allylzirconation and alkenylzirconation of alkynes.[17] For example, when alkenylzirconocene **2n** and **2o** generated from zirconocene–alkyne complexes and diallyl ester were adopted, skipped diencarboxylic acids **3n** and **3o** were yielded, respectively (Table 3, entries 1–2). When dienylzirconocene ethanolyzed from the corresponding zirconacyclopentadiene was employed, tetrasubstituted diencarboxylic acid **3p** was obtained (entry 3). Furthermore, when alkenylzirconocene **2q** and **2r** produced by the reaction of the zirconacyclopentene with ethoxyethene were employed, disubstituted diencarboxylic acid **3q** and **3r** were afforded, respectively (entries 4–5). When alkenylzirconocene **2s** and **2t** yielded from the zirconocene–alkyne complex and 4-bromobut-1-ene or 3-chlorobut-1-ene were subjected, the corresponding α,β-unsaturated carboxylic acid **3s** and **3t** were obtained in 65% and 58% yields, respectively (entries 6–7). In addition, the vinylzirconocene species **2u** resulting from the hydrozirconation of alkynes employing Schwartz' reagent[18] could also proceed in a carboxylation with CO_2 under the optimized conditions to afford the corresponding α,β-unsaturated carboxylic acid **3u** (entry 8).

Table 2. (IMes)CuCl-Catalyzed Carboxylation of Alkenylzirconocenes with CO_2[a]

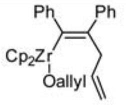
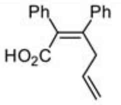
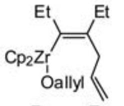
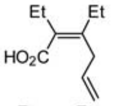
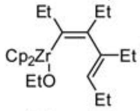
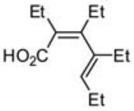
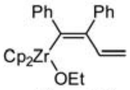
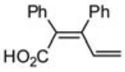
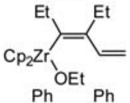
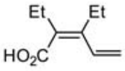
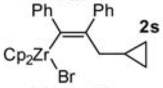
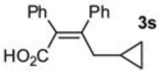
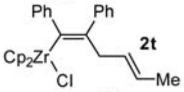
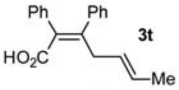
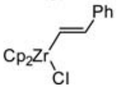
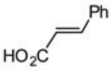


entry	alkenylzirconocene		product		yield/%[b]
1		**2a**		**3a**	70
2		**2b**		**3b**	61
3		**2c**		**3c**	67
4		**2d**		**3d**	52
5		**2e**		**3e**	46
6		**2f**		**3f**	66
7		**2g**		**3g**	77
8		**2h**		**3h**	57
9		**2i**		**3i**	72
10		**2j**		**3j**	73
11		**2k**		**3k**	50
12		**2l**		**3l**	62
13		**2m**		**3m**	49

[a] Reaction conditions: alkenylzirconocene **2** prepared *in situ* from alkyne (0.5 mmol), (IMes)CuCl (0.05 mmol).

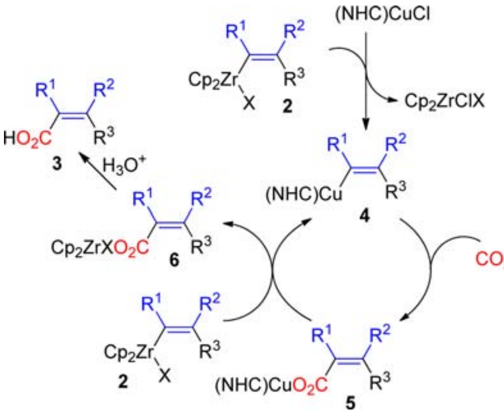
On the basis of the results, a possible reaction mechanism of the present catalytic carboxylation of alkenylzirconocene species with CO_2 is illustrated in Scheme 2. First, transmetalation from the Zr–C bond to the Cu–C bond occurs to yield alkenylcopper species **4**. Then nucleophilic addition of the alkenylcopper **4** to CO_2 produces copper carboxylate **5**, which upon metathesis with the alkenylzirconocene species **2** could regenerate alkenylcopper **4** and release zirconocene salt **6**. The zirconocene salt **6** would generate the α,β-unsaturated carboxylic acid **3** after hydrolysis.

Table 3. (IMes)CuCl-Catalyzed Carboxylation of Alkenylzirconocenes with CO_2[a]

entry	alkenylzirconocene	product	yield/%[b]
1	 **2n**	 **3n**	73
2	 **2o**	 **3o**	76
3	 **2p**	 **3p**	61
4	 **2q**	 **3q**	52
5	 **2r**	 **3r**	45
6	 **2s**	 **3s**	65
7	 **2t**	 **3t**	58
8	 **2u**	 **3u**	48

[a]Reaction conditions: alkenylzirconocene **2** prepared *in situ* from alkyne (0.5 mmol), (IMes)CuCl (0.05 mmol), CO_2 (1 atm), room temperature, 24 h.

Scheme 2. A Possible Mechanism for (NHC)CuCl-Catalyzed Carboxylation of Alkenylzirconocene with CO_2



In summary, we have developed the (NHC)CuC-catalyzed carboxylation reaction of alkenylzirconocenes with CO_2 under mild conditions. As the alkenylzirconocenes are easily available from carbozirconation of alkynes, various trisubstituted *α,β*-unsaturated carboxylic acids are prepared in this reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02619.

Full experiment procedure, spectra data, and NMR charts (PDF)

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Notes

The authors declare no competing financial interest.

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